

AFG GP1642

PTO/SB/17 (12-98)
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Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

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FEE TRANSMITTAL for FY 1999

Patent fees are subject to annual revision.
Small Entity payments must be supported by a small entity statement,
otherwise large entity fees must be paid. See Forms PTO/SB/09-12.

TOTAL AMOUNT OF PAYMENT (\$585.00)

Complete if Known

Application Number 08/259,321
Filing Date June 10, 1994
First Named Inventor Alireza Rezaie
Examiner Name N. Johnson
Group / Art Unit 1642
Attorney Docket No. OMRP 106 CIP

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TECH CENTER 1600/2900

METHOD OF PAYMENT (check one)		FEE CALCULATION (continued)																																																																																																																																																																	
<p>1. <input type="checkbox"/> The Commissioner is hereby authorized to charge indicated fees and credit any over payments to:</p> <p>Deposit Account Number <u>01-2507</u></p> <p>Deposit Account Name <u>Arnall Golden & Gregory, LLP</u></p> <p><input checked="" type="checkbox"/> Charge Any Additional Fee Required Under 37 CFR 1.16 and 1.17</p> <p>2. <input checked="" type="checkbox"/> Payment Enclosed: <input checked="" type="checkbox"/> Check <input type="checkbox"/> Money Order <input type="checkbox"/> Other</p>		<p>3. ADDITIONAL FEES</p> <table border="1"><thead><tr><th>Large Entity Fee Code</th><th>Small Entity Fee Code</th><th>Fee Description</th><th>Fee Paid</th></tr></thead><tbody><tr><td>105</td><td>130</td><td>205</td><td>65</td><td>Surcharge - late filing fee or oath</td><td></td></tr><tr><td>127</td><td>50</td><td>227</td><td>25</td><td>Surcharge - late provisional filing fee or cover sheet.</td><td></td></tr><tr><td>139</td><td>130</td><td>139</td><td>130</td><td>Non-English specification</td><td></td></tr><tr><td>147</td><td>2,520</td><td>147</td><td>2,520</td><td>For filing a request for reexamination</td><td></td></tr><tr><td>112</td><td>920*</td><td>112</td><td>920*</td><td>Requesting publication of SIR prior to Examiner action</td><td></td></tr><tr><td>113</td><td>1,840*</td><td>113</td><td>1,840*</td><td>Requesting publication of SIR after Examiner action</td><td></td></tr><tr><td>115</td><td>110</td><td>215</td><td>55</td><td>Extension for reply within first month</td><td></td></tr><tr><td>116</td><td>380</td><td>216</td><td>190</td><td>Extension for reply within second month</td><td></td></tr><tr><td>117</td><td>870</td><td>217</td><td>435</td><td>Extension for reply within third month</td><td>435.00</td></tr><tr><td>118</td><td>1,360</td><td>218</td><td>680</td><td>Extension for reply within fourth month</td><td></td></tr><tr><td>128</td><td>1,850</td><td>228</td><td>925</td><td>Extension for reply within fifth month</td><td></td></tr><tr><td>119</td><td>300</td><td>219</td><td>150</td><td>Notice of Appeal</td><td></td></tr><tr><td>120</td><td>300</td><td>220</td><td>150</td><td>Filing a brief in support of an appeal</td><td>150.00</td></tr><tr><td>121</td><td>260</td><td>221</td><td>130</td><td>Request for oral hearing</td><td></td></tr><tr><td>138</td><td>1,510</td><td>138</td><td>1,510</td><td>Petition to institute a public use proceeding</td><td></td></tr><tr><td>140</td><td>110</td><td>240</td><td>55</td><td>Petition to revive - unavoidable</td><td></td></tr><tr><td>141</td><td>1,210</td><td>241</td><td>605</td><td>Petition to revive - unintentional</td><td></td></tr><tr><td>142</td><td>1,210</td><td>242</td><td>605</td><td>Utility issue fee (or reissue)</td><td></td></tr><tr><td>143</td><td>430</td><td>243</td><td>215</td><td>Design issue fee</td><td></td></tr><tr><td>144</td><td>580</td><td>244</td><td>290</td><td>Plant issue fee</td><td></td></tr><tr><td>122</td><td>130</td><td>122</td><td>130</td><td>Petitions to the Commissioner</td><td></td></tr><tr><td>123</td><td>50</td><td>123</td><td>50</td><td>Petitions related to provisional applications</td><td></td></tr><tr><td>126</td><td>240</td><td>126</td><td>240</td><td>Submission of Information Disclosure Stmt</td><td></td></tr><tr><td>581</td><td>40</td><td>581</td><td>40</td><td>Recording each patent assignment per property (times number of properties)</td><td></td></tr><tr><td>146</td><td>760</td><td>246</td><td>380</td><td>Filing a submission after final rejection (37 CFR 1.129(a))</td><td></td></tr><tr><td>149</td><td>760</td><td>249</td><td>380</td><td>For each additional invention to be examined (37 CFR 1.129(b))</td><td></td></tr></tbody></table> <p>Other fee (specify) _____</p> <p>**Represents the difference between the fee for a <input type="checkbox"/> month extension of time and a <input type="checkbox"/> month extension of time.</p> <p>Reduced by Basic Filing Fee Paid</p> <p>SUBTOTAL (3) (\$585.00)</p>		Large Entity Fee Code	Small Entity Fee Code	Fee Description	Fee Paid	105	130	205	65	Surcharge - late filing fee or oath		127	50	227	25	Surcharge - late provisional filing fee or cover sheet.		139	130	139	130	Non-English specification		147	2,520	147	2,520	For filing a request for reexamination		112	920*	112	920*	Requesting publication of SIR prior to Examiner action		113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action		115	110	215	55	Extension for reply within first month		116	380	216	190	Extension for reply within second month		117	870	217	435	Extension for reply within third month	435.00	118	1,360	218	680	Extension for reply within fourth month		128	1,850	228	925	Extension for reply within fifth month		119	300	219	150	Notice of Appeal		120	300	220	150	Filing a brief in support of an appeal	150.00	121	260	221	130	Request for oral hearing		138	1,510	138	1,510	Petition to institute a public use proceeding		140	110	240	55	Petition to revive - unavoidable		141	1,210	241	605	Petition to revive - unintentional		142	1,210	242	605	Utility issue fee (or reissue)		143	430	243	215	Design issue fee		144	580	244	290	Plant issue fee		122	130	122	130	Petitions to the Commissioner		123	50	123	50	Petitions related to provisional applications		126	240	126	240	Submission of Information Disclosure Stmt		581	40	581	40	Recording each patent assignment per property (times number of properties)		146	760	246	380	Filing a submission after final rejection (37 CFR 1.129(a))		149	760	249	380	For each additional invention to be examined (37 CFR 1.129(b))	
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SUBMITTED BY		Complete (if applicable)	
Typed or Printed Name	<u>Patrea L. Pabst</u>	Reg. Number	<u>31,284</u>
Signature	<u>[Signature]</u>	Deposit Account User ID	<u>01-2507</u>
Date	<u>11/30/99</u>		

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

In re application of: Alireza Rezaie and Charles T. Esmon

Serial No.: 08/259,321

Filed: June 10, 1994

For: CALCIUM BINDING RECOMBINANT ANTIBODY AGAINST PROTEIN C

ASSISTANT COMMISSIONER FOR PATENTS
Washington, D.C. 20231

Sir:

Transmitted herewith is an amendment to the above-identified application.

☒ Small entity status of this application under 37 CFR 1.9 and 1.27 has been established by a verified statement previously submitted.☐ A verified statement to establish small entity status under 37 CFR 1.9 and 1.27 is enclosed.☒ No additional fee is required.

The fee has been calculated as shown below:

(Col. 1)			(Col. 2)		(Col. 3)		SMALL ENTITY		OTHER THAN A SMALL ENTITY	
	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NO. PREVIOUSLY PAID FOR		PRESENT EXTRA		RATE	ADDIT. FEE	RATE	ADDIT. FEE
TOTAL	13	MINUS	20	=	0		X =	\$ 0	x =	\$
INDEP	2	MINUS	3	=	0		x =	\$ 0	x =	\$
<input checked="" type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEP. CLAIM							+	\$	+	\$
TOTAL ADDIT. FEE								\$ 0	or TOTAL	\$

* If the entry in Col. 1 is less than the entry in Col. 2, write "0" in Col. 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, write "20" in this space.

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, write "3" in this space.

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found from the equivalent box in Col.1 of a prior amendment or the number of claims originally filed.

☒ Please charge my Deposit Account No. 01-2507 in the amount of \$ 55.00.
A duplicate copy of this sheet is attached.☐ Check in the amount of \$ _____ is attached.☒ The Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 01-2507.
A duplicate copy of this sheet is enclosed.☒ Any additional filing fees under 37 CFR 1.16 for the presentation of extra claims.☒ Any patent application processing fees under 37 CFR 1.17.

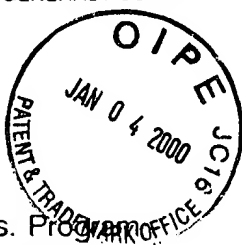
Respectfully submitted,

Patrea L. Pabst, Reg. No. 31,284



LU...J UNIVERSITY
DEPARTMENT OF CLINICAL CHEMISTRY
MALMÖ GENERAL HOSPITAL

Malmö 92 01 28.



Dr. Naomi Esmon
Cardiovasc. Biol. Res. Program
Oklahoma Med. Res. Found.
825 N. E. 13th Street
Oklahoma City, OK 73104
USA



Dear Naomi,

Thank you for your letter of Jan 14th. I do apologize for not having answered it before but I have had a very bad influenza for more than a week.

As you know we have made several sets of monoclonal antibodies against human protein C, even one that is calcium-dependent and unfortunately called HPC-4 just like your antibody. However, our antibody is of course entirely different from your HPC-4 and recognizes an epitope in the first EGF-like module. Among the monoclonal antibodies we have made there are several against the activation peptide that do not recognize the active enzyme and as far as I recall block activation. However, none of our activation peptide recognizing monoclonal antibodies is calcium dependent. My experience is based on at least four different fusions and we have isolated and characterized at least twenty different stable monoclonal antibodies against protein C.

Based on the considerable experience we have of monoclonal antibodies against human protein C and from what I have read in the literature I am convinced that your antibody, labelled HPC-4 is truly unique and has very unusual properties, particularly with regard to the calcium binding properties.

Björn has read the letter. He agrees and sends his best regards.

With all the best wishes for you and Chuck.

Sincerely,

Johan Stenflo

Postal address
Malmö General Hospital
S-214 01 MALMÖ, SWEDEN

Telephone
46-40-331424
331000

Fax
46-40-929023



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Alireaz Rezaie and Charles T. Esmon

Serial No.: 08/259,321

Group Art Unit: 1642

Filed: June 10, 1994

Examiner: N. Johnson

For: ~~CALCIUM-BINDING RECOMBINANT ANTIBODY AGAINST~~
~~PROTEIN C~~

Assistant Commissioner
of Patents
Washington, D.C. 20231

PETITION FOR EXTENSION OF TIME

Sir:

Pursuant to Public Law 97-247, Section 8, and 37 C.F.R. 1.136(a) applicants herewith petition that the period for response to the Office Action mailed on August 31, 1998, in the above-identified application be extended for one month, to and including December 31, 1998. The appropriate fee for this extension under 37 C.F.R. § 1.17 is \$55.00 for a small entity. The Commissioner is authorized to charge this fee to our Deposit Account No.01-2507.

Serial No. 08/259,321
Filed: June 10, 19984
PETITION FOR EXTENSION OF TIME



If this fee is insufficient, please charge our Deposit Order Account No. 01-2507. To facilitate this process, applicants have enclosed a duplicate of this document.

Respectfully submitted,

A handwritten signature in dark ink, appearing to be "Patrea L. Pabst", written over a horizontal line.

Patrea L. Pabst
Reg. No. 31,284

Date: December 31, 1998
ARNALL GOLDEN & GREGORY, LLP
2800 One Atlantic Center
1201 W. Peachtree Street
Atlanta, GA 30309-3450
(404) 873-8794

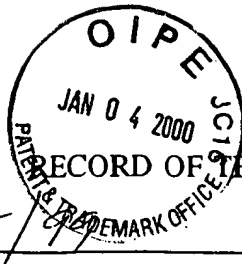
CERTIFICATE OF MAILING (37 CFR § 1.8a)

I hereby certify that this Petition for Extension of Time, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner of Patents, Washington, D.C. 20231.

Date: December 31, 1998

A handwritten signature in dark ink, appearing to be "Patrea L. Pabst", written over a horizontal line.

Patrea L. Pabst



RECORD OF TELEPHONE CONVERSATION

DATE:

4/5/99

CLIENT/MATTER NO: OMRF 106 CIP DOCKET NO: 20487/106

PERSON SPOKEN TO: Nancy Johnson

PHONE NO: 703-305-5860

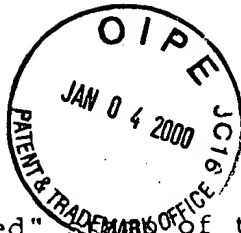
FAX NO.: 703-308-4426

RE: 08/259,321

Left message 4/2/99

Talked to Examiner - She said the declarations were not with the package when it got to her. She asked me to fax them to her, which I have done.

2



The "Received" stamp of the Patent Office imprinted hereon acknowledges the filing of:

Applicant: Alireza Rezaie and Charles T. Esmon

Serial & Docket No. 08/259,321 OMRF 106 CIP

Filed: June 10, 1994

Papers Submitted:

Amendment with Certificate of Mailing under 37 CFR 1.8(a) (in duplicate); Petition for One Month Extension of Time with Certificate of Mailing (in duplicate); Copies of 7 Declarations that were filed in the parent application; Fee Sheet (in duplicate); Authorization to Charge Deposit Account.

Date: December 31, 1998

20487/106

By: Patrea L. Pabst, Reg. No. 31,284

FD

1-6-99



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Alireza Rezaie and Charles T. Esmon

Serial No.: 08/259,321

Group Art Unit: 1642

Filed: June 10, 1994

Examiner: N.Johnson

For: CALCIUM BINDING RECOMBINANT ANTIBODY AGAINST PROTEIN C

Assistant Commissioner of Patents
Washington, D.C. 20231

AMENDMENT

Sir:

Responsive to the Office Action mailed August 31, 1998, please amend the application as follows and consider the following remarks and accompanying materials. A Petition for an Extension of Time for one month, up to and including December 31, 1998, and the appropriate fee for a small entity, are enclosed.

In the Claims

3. (four times amended) The antibody of claim 1 which is humanized [by the inclusion of a human constant domain or framework regions of the variable domain].
biological fluid.

Remarks

Sequence Listing

The Examiner has objected to the reference in claims 2 and 15 to a portion of a longer amino acid sequence provided in and with the application as originally filed, in computer

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FILED: JUNE 10, 1994
AMENDMENT

readable form. It is believed that the Sequence Listing is in compliance with 37 C.F.R.

§1.181(d). The requirement is that the sequence must be present in a Sequence Listing in computer readable form; not that each portion described or claimed be presented in a **separate** Sequence Listing. To do so would result in unnecessary duplication and paperwork for all parties. Each of the claimed sequences present in claims 2 and 15 are described in a Sequence Listing.

Rejections under 35 U.S.C. §112

Claims 1-3, 5, 7, 8, 14, 15, and 17-21 were rejected on the basis that the reference to humanized in claims 1 and 15, with a more narrow definition in claim 3 (incorrectly referenced in the office action as claim 2) rendered the claims indefinite. This rejection is traversed but also rendered moot by deletion of the objected to language in claim 3. The corresponding claim dependent on claim 15 did not include this language.

Double patenting Rejection

Claims 1, 2, 5, 6, 8, 14, 15 and 20 under the doctrine of obviousness-type double patenting over U.S. Patent No. 5,202,253 to Esmon, et al. in view of Morrison, Science 229, 1201-1207 (1985) or WO90/07861 by Protein Design Labs, Inc. ("Queen"). This rejection is respectfully traversed and is discussed in more detail below in regard to the rejections under 35 U.S.C. §103.

Esmon discloses a unique monoclonal murine antibody reactive with two elements: calcium and a peptide present in protein C. It was not obvious from Esmon alone or in

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FILED: JUNE 10, 1994
AMENDMENT

combination with the references detailing preparation of monoclonal antibodies and humanized antibodies that one could humanize this unique monoclonal antibody and still retain the unique reactivity.

Rejections under 35 U.S.C. §103

Claims 1, 2, 3, 5, 7, 8, 14, 15, and 17-21 were rejected under 35 U.S.C. §103 as obvious over U.S. Patent No. 5,202,253 or 5,147,638 to Esmon, et al, D'Angelo, et al., J. Clin. Invest. 77, 416-425 (1986) or Stearns, et al., J. Biol. Chem. 263(2) 826-832 (1988) in view of Morrison, Science 229, 1201-1207 (1985) or WO90/07861 by Protein Design Labs, Inc. ("Queen"). These rejections are respectfully traversed.

The Claimed Antibodies are Distinct and not Predictable from the Prior Art

U.S. Patent Nos. 5,202,253 and 5,147,638

Neither U.S. Patent No. 5,202,253 nor 5,147,638 disclose nor claim a recombinant antibody; the patent is drawn to a naturally occurring murine antibody. The '253 reference does not enable a recombinant antibody, and certainly provides no guidance for how the antibody could be humanized. As demonstrated by the enclosed copies of the seven Declarations under 37 C.F.R. §1.132 filed during the prosecution of these applications, the claimed murine antibody was totally unique and that was why it was patentable. Moreover, it was impossible to predict that one could obtain another antibody with the same kind of reactivity.

Stearns

Stearns was cited as prior art to, and overcome during the prosecution of, the claimed

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murine monoclonal antibodies in the '638 and '253 patents. Stearns reported on the properties of the claimed murine monoclonal antibody but was determined not to enable one to make and use the antibody due to the unique characteristics of the antibody. If the article could not enable and make obvious the antibody it described, it certainly could not enable and make obvious cloning and expression of a recombinant antibody sharing only the portion of the antibody conferring the unique specificity as claimed. No amino acid or nucleotide sequence is provided, nor would it be obvious from the protein.

D'Angelo

D'Angelo is an even less illuminating description of the murine monoclonal antibody referred to as HPC4, than the Stearns paper. Again, there is nothing that would enable the HPC4 antibody, much less cloning and manipulation so that the antibody could be expressed in either bacterial cells or incorporating human amino acid sequences.

Morrison and Queen

Morrison or Queen do not make up for these deficiencies. Neither provides the enablement to clone HPC4, nor provides any basis for believing that such a unique antibody could be cloned and still behave in its usual calcium dependent manner. It is clear that under §103 the art must not only motivate one to modify that which is disclosed in the prior art as applicants have done, but that there must be a reasonable expectation of success in doing so. The Examiner can point to no such support, and it is in fact contradicted by the numerous declarations filed during the prosecution of the parent applications, even more strongly

supporting the patentability of the claimed humanized or recombinant antibodies.

Summary

An antibody secreted by a murine hybridoma from murine antibody genes is not the same as the claimed antibody, which is either expressed in bacterial or insect cells or has been humanized. As evidenced by the prosecution history in the '253 case, numerous experts submitted declarations under oath that even with undue experimentation they were unable to make by standard techniques monoclonal antibodies having the unique specificity of HPC-4: binding with one part of the antibody a peptide epitope and binding with another part of the antibody calcium. Until one had actually cloned the nucleotide sequence encoding HPC-4 and expressed it, it was not possible to predict that the isolated nucleotide sequence encoded HPC-4, much less whether it would be expressed in functional form. Recombinant fragments have been expressed in bacteria and shown to have the requisite binding activity. Humanized antibodies having the same specificity have now been made using standard techniques, based on the disclosed nucleotide sequence, by Genentech. In the absence of the nucleotide sequence, one cannot modify and genetically engineer the antibody to include non-murine amino acid sequence.

The Examiner's position is that the nucleotide sequence is obvious from the prior disclosure of the protein, i.e., the HPC-4 antibody. In the absence of the nucleotide sequence, one could not make the claimed antibody. It remains the position of the undersigned that the Court of Appeals in In re Deuel, 34 USPQ2d 1210 (Fed. Cir. 1995) that merely having the

protein, or even some amino acid sequence (which is not described in the claims of the issued patent) would not be sufficient. The examiner has cited no art that discloses or makes obvious the amino acid sequence encoded by the recited nucleic acid. The art which has been cited by the Examiner discloses general methods to make chimeric antibodies. This would not provide one skilled in the art with the methodology and a reasonable expectation of success that one could clone the hypervariable region of the HPC4 antibody, insert the cloned genes into an expression vector, and express antibody or antibody fragments having the requisite binding affinity. Even though the claimed subject matter is an antibody, the antibody **cannot be made except by expression of the nucleotide sequence**; accordingly, the antibody cannot be obvious from the naturally occurring antibody.

There are two basis on which the claimed antibodies are not obvious:

- (1) the nucleotide sequence encoding the antibody was not known and the protein sequence of the antibody was not known, and
- (2) the specificity of the antibody required the presence of two distinct molecules: calcium and a peptide epitope, a highly unusual situation for antibodies.

Applicants had attempted to make antibody fragments which had the requisite binding activity and found that the cleavage reactions generated many products, with loss of most activity. The definition of the hypervariable region, which was determined by cloning, was critical to construction and expression of defined portions of HPC4 and to humanization of the antibody. One skilled in the art simply could not have any basis for determining whether or not

an antibody with the unique specificity of the HPC4 antibody could be cloned and this specificity expressed in a recombinant molecule. The Examiner has cited no evidence that one skilled in the art had ever attempted to clone such an antibody, much less had any success. The key to sustaining an obviousness rejection in this kind of situation is **not whether it was obvious to try, but whether one skilled in the art would have an expectation of success.** HPC4 was a highly unusual antibody. As demonstrated by the declarations submitted in the prosecution of the patents claiming HPC4, unlike most monoclonals, HPC4 was impossible to duplicate. Calcium dependent antibodies immunoreactive to protein C, obtained by other parties, simply did not share the unique reactivity where calcium is essential to binding - merely having calcium present to alter binding **affinity** was not enough. This unique reactivity was obtained in the cloned, recombinant antibody - but this success, not well understood even after cloning, could not have been predicted.

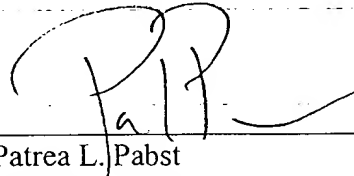
The same general analysis as under §103 is applied under the doctrine of obviousness-type double patenting, but with regard solely to the issue of whether the claims in this application are obvious over the claims in the issued patent. For the same reasons that the claims are not obvious in view of the disclosures of these patents, they are even less obvious from the claims. The claimed murine antibody, and methods of use thereof, do not make obvious the nucleotide sequence required to make the recombinant antibody, nor is it predictable that even if one did clone the antibody, that the unique binding characteristics of HPC-4 would be transferred to the recombinant antibody.

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Allowance of all claims 1, 3-5, 7, 8, 14, 15, and 17-21, as amended, is earnestly solicited.

All claims as pending upon entry of this amendment are attached in an appendix for the convenience of the examiner.

Respectfully submitted,

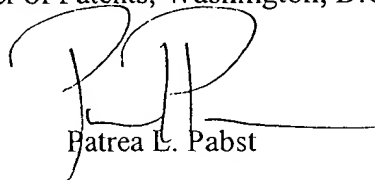


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Certificate of Mailing under 37 CFR § 1.8(a)

I hereby certify that this Amendment is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner of Patents, Washington, D.C. 20231.



Patrea L. Pabst

Date: December 31, 1998



APPENDIX: Claims as pending upon entry of this amendment

1. (four times amended) A recombinant Ca^{2+} dependent monoclonal antibody or antibody fragment including a heavy chain and a light chain, wherein the antibody or antibody fragment comprise the hypervariable regions of the monoclonal antibody produced by the hybridoma deposited with the American Type Culture Collection as ATCC No. HB 9892 which bind an epitope in the activation peptide region of the heavy chain of Protein C defined by E D Q V D P R L I D G K (Sequence ID No. 1) and calcium ions, where the antibody and antibody fragment inhibit Protein C activation by thrombin-thrombomodulin, and wherein the antibody and antibody fragment are expressed in bacterial or insect cells or is humanized.

2. (amended) The antibody of claim 1 comprising an amino acid sequence selected from the group consisting of:

MGRLLLLLIAPAYVLSQ VTLKESGPGI LQPSQTLTLT CSLSGFSLRT
SGMGVGWIRQ PSGKGLEWLA HIWWDDDKRY NPVLKSRLII SKDTSRKQVF
LKIASVDTAD TATYYCVRMM DDYDAMDYWG QGTSVTVSS (Sequence ID No. 10);
MDFQVQIFSF LLISASVIMS RGQIILTQSP AIMSASLGEE ITLTCSATSS VTYVHWYQQK
SGTSPKLLIY GTSNLAGSVP SRFSGSGSGT FYSLTVSSVE AEDAADYYCH
QWNSYPHTFG GGTKLEIKR (Sequence ID No. 12); Q VTLKESGPGI LQPSQTLTLT
CSLSGFSLRT SGMGVGWIRQ PSGKGLEWLA HIWWDDDKRY NPVLKSRLII
SKDTSRKQVF LKIASVDTAD TATYYCVRMM DDYDAMDYWG QGTSVTVSS (amino
acids 20-139 of Sequence ID No. 10) and QIILTQSP AIMSASLGEE ITLTCSATSS
VTYVHWYQQK SGTSPKLLIY GTSNLAGSVP SRFSGSGSGT FYSLTVSSVE
AEDAADYYCH QWNSYPHTFG GGTKLEIKR (amino acids 23-129 of Sequence ID No. 12).

3. (four times amended) The antibody of claim 1 which is humanized [by the inclusion of a human constant domain or framework regions of the variable domain].

5. (amended) A composition comprising the antibody of claim 1 in combination with a pharmaceutically acceptable carrier for administration to a patient.

7. (amended) The antibody of claim 1 having a detectable label directly bound to the antibody.

8. (twice amended) The antibody of claim 1 immobilized to a substrate which does not interfere with binding of the antibody to protein C in combination with calcium ions, wherein the immobilized antibody is suitable for purification of protein C from a biological fluid.

14. (four times amended) A method of making a recombinant Ca^{2+} dependent monoclonal antibody which binds an epitope in the activation peptide region of the heavy chain of Protein C defined by E D Q V D P R L I D G K (Sequence ID No. 1) and calcium ions, where the antibody inhibits Protein C activation by thrombin-thrombomodulin, by expressing nucleotide molecules encoding the hypervariable region of the heavy and light chains of the monoclonal antibody expressed by the hybridoma deposited with the American Type Culture Collection as ATCC No. HB 9892 in bacteria or insect cells.

15. (amended) The method of claim 14 wherein the antibody comprises an amino

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acid sequence selected from the group consisting of:

MGRLLLLL LIAPAYVLSQ VTLKESGPGI LQPSQTLTLT CSLSGFSLRT
SGMGVGWIRQ PSGKGLEWLA HIWWDDDKRY NPVLKSRLII SKDTSRKQVF
LKIASVDTAD TATYYCVRMM DDYDAMDYWG QGTSVTVSS (Sequence ID No. 10);
MDFQVQIFSF LLISASVIMS RGQILTQSP AIMSASLGEE ITLTCSATSS VTYVHWYQQK
SGTSPKLLIY GTSNLAGSVP SRFSGSGSGT FYSLTVSSVE AEDAADYYCH
QWNSYPHTFG GGTKLEIKR (Sequence ID No. 12); Q VTLKESGPGI LQPSQTLTLT
CSLSGFSLRT SGMGVGWIRQ PSGKGLEWLA HIWWDDDKRY NPVLKSRLII
SKDTSRKQVF LKIASVDTAD TATYYCVRMM DDYDAMDYWG QGTSVTVSS (amino
acids 20-139 of Sequence ID No. 10) and QILTQSP AIMSASLGEE ITLTCSATSS
VTYVHWYQQK SGTSPKLLIY GTSNLAGSVP SRFSGSGSGT FYSLTVSSVE
AEDAADYYCH QWNSYPHTFG GGTKLEIKR (amino acids 23-129 of Sequence ID No. 12).

17. (four times amended) The method of claim 14 wherein the antibody is humanized.
18. (amended) The method of claim 14 further comprising directly binding detectable label to the antibody.
19. (amended) The method of claim 14 further comprising immobilizing the antibody to a substrate which does not interfere with binding of the antibody to protein C in combination with calcium ions, wherein the immobilized antibody is suitable for purification of protein C from a biological fluid.
20. (amended) The recombinant antibody of claim 1 having coupled thereto a peptide sequence.
21. (amended) The method of claim 14 wherein the nucleotide sequence encoding the recombinant antibody is ligated to a sequence encoding a peptide and the ligated nucleotide sequence is expressed in an expression system.